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The nasal microbiome in granulomatosis with polyangiitis

Granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis) is a chronic relapsing autoimmune disease. Most patients are affected by ear, nose and throat (ENT) manifestations [1], which may lead to chronic epistaxis, crusting, impaired olfaction and possibly deformational changes (e.g. saddle nose deformity). Nasal colonization with *Staphylococcus aureus* may be a substantial environmental influence implicated in the etiopathogenesis of GPA [2]. Of importance, *Staphylococcus aureus* represents an important opportunistic pathogen and permanently lives as a commensal in 20–30 % of the general population and intermittently in approximately 60 %. Colonization with *Staphylococcus aureus* is an accepted risk factor for infections, which is independent of the particular strain [3]. In patients with GPA, the presence of chronic *Staphylococcus aureus* colonization examined by nasal swab cultures indicates an independent risk factor for relapse of GPA when compared to non-carriers. In this large single centre (AE) investigation the percentage of chronic carriers was 63 %. Chronic carriers were defined as the presence of positive cultures in ≥75 % [4]. A prospective, randomized, placebo-controlled study to evaluate the efficacy of trimethoprim-sulfamethoxazole twice daily for 24 months revealed a significant reduction of disease relapses in patients with GPA. In addition, a significant reduction of respiratory and non-respiratory tract infections was reported in patients with trimethoprim-sulfamethoxazole treatment [5]. A recent study showed significantly higher nasal *Staphylococcus aureus* carriage in patients with GPA (72 %) compared to chronic rhinosinusitis patients (28 %) and healthy controls. Patients with chronic nasal *Staphylococcus aureus* carriage had significantly higher endoscopically proven endonasal activity, significantly more often initial manifestation in the ENT tract and a non-significantly higher relapse rate (p = 0.052) than patients without carriage [6]. Notably, the pathogenicity of *Staphylococcus aureus* in GPA patients may be at least in part attributed to the production of pyrogenic toxins. Diverse antigens of *Staphylococcus aureus* have been identified in patients with GPA. Among these superantigens (SAg), the toxic shock syndrome toxin-1 (tsst-1) is one of the most virulent. A retrospective longitudinal cohort study revealed that a high proportion of GPA patients (>70 %) carried at least one *Staphylococcus aureus* SAg. In general, the presence of *Staphylococcus aureus* was accompanied by a higher risk for relapse, while the risk was modulated by the type of SAg, with tsst-1 being most strongly associated with disease relapse. The number of patients positive for *Staphylococcus aureus* tsst-1 was significantly higher with 36 % compared to the general population [7].

Rituximab, a monoclonal antibody targeting CD20 bearing cells, has been licensed in the treatment of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Although non-inferior in both randomized, controlled trials, adverse events (e.g. serious infections) were comparable [8, 9]. In an elegant retrospective study, Besada et al. investigated the role of maintenance rituximab treatment. Chronic carriage rates were not influenced by the treatment; however, an increase in transient *Staphylococcus aureus* carriage could be observed with virtually no effect on infections, relapse or hypogammaglobulinemia [10].

Examination of nasal epithelial cells obtained from patients with GPA and normal controls indicated a significant up-regulation of granulocyte-colony stimulating factor, whereas interleukin-8 concentrations were reduced. After stimulation with supernatants of *Staphylococcus aureus,* GPA patients displayed a significantly lower interleukin-8 secretion and a diminished dynamic range of response towards the stimuli. These findings indicate an impaired inflammatory response and a reduced response to a microbial stimulation leading to alterations of the microbial composition of the nostrils [11]. Antimicrobial peptides from patients with either *Staphylococcus aureus* colonization or negatives were assessed by ELISA. In patients with colonization significantly higher levels of LL-37 could be detected and after stimulation with *Staphylococcus aureus* significantly higher levels of LL-37 and human ß-defensin 3 could be detected in the supernatant of nasal epithelial cells of GPA patients [12]. A transcriptomic approach revealed differential expression of 10 transcripts including antimicrobial transcripts, such as human beta-defensin 1, lysozyme and human beta-defensin 4; however, the expression of these transcripts did not correlate with *Staphylococcus aureus* colonization [13]. Further investigations of nasal epithelia revealed an impaired ciliary beat frequency which almost stagnated after 24 h. A significant correlation of impaired ciliary beat frequency with the cumulative number of immunosuppressive agents could be found [14]. More recently, a study indicated lower anti staphylococcal IgG

levels against 59 *Staphylococcus aureus* antigens in GPA patients compared to healthy controls despite similar overall IgG levels. Moreover, an increased frequency of resistant *Staphylococcus aureus* strains towards trimethoprim-sulfamethoxazole or ciprofloxacin was observed over time [15]. The former finding was not correlated with rituximab treatment, which is known to impair antibody response as shown in vaccination studies.

Taken together, a pivotal role of *Staphylococcus aureus* carriage in GPA has been proposed by several authors. The high number of chronic colonization exceeds the number observed in the general population. Several pathophysiological considerations have been published which may explain the pathogenicity of *Staphylococcus aureus* in GPA, mainly a reduced IgG response towards *Staphylococcus aureus* and several molecular alterations along with an abundance of antimicrobial peptides. Novel techniques, especially microbiome analysis using either 16 S PCR or whole shotgun sequencing will allow us to decipher the causality whether *Staphylococcus aureus* is implicated in the etiopathogenesis or colonization is a consequence of active vasculitis/damage.

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Compliance with ethical guidelines

Conflict of interest. A. Kronbichler states that there are no conflicts of interest.

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